II. REMARKS

Upon entry of the amendment, claims 1, 7 to 9, 12 to 14, 19, 22 to 26, and 30 to 36 will be pending. A marked copy of the claims showing the amendments is attached hereto as Exhibit A.

A. Regarding the Amendments

Claims 15 to 17, 19 to 21, and 27 to 29 are canceled herein without disclaimer, and without prejudice to Applicant pursuing prosecution of subject matter encompassed within one or more of the claims in an application claiming the benefit of priority of the subject application.

Claim 1 has been amended to more clearly indicate that the malignant cells to be treated are associated with "decreased transcription of a 5'ALT polynucleotide comprising exon 2 of a p15 gene" and that the method includes "administering locally at a site of the cells" a "polynucleotide comprising 5'ALT operatively linked to exon 2 of the p15 gene." In view of this amendment to claim 1, new claim 34 has been added, and is directed to subject matter previously encompassed within claim 1, but more specifically directed to a "5'ALT polynucleotide comprising exons 2 and 3 of a p16 gene." The amendment to claim 1 and new claim 34 are supported, for example, at page 5, lines 17-19; page 29, lines 3-6 (first full sentence); and page 43, lines 8-12 (last sentence of first paragraph).

Claim 9 has been amended to more clearly indicate that the methylation of the p16 gene results in "decreased" p16 expression, and that the method of treatment includes "administering locally at a site of the malignant cells exhibiting decreased p16 gene expression" a "polynucleotide comprising 5'ALT operatively linked to exons 2 and 3 of the p16 gene". The amendment and new claim are supported, for example, at page 5, lines 17-19; page 43, lines 8-12 (last sentence of first paragraph); and page 72, last paragraph.

Claim 13, which depends from claim 9, has been amended such that the language of claim 13 corresponds to that of amended claim 9. As such, the amendment to claim 13 merely addresses a formality.

Claims 18 and 26 have been amended to more clearly indicate that the malignant cells are characterized by decreased expression of a polynucleotide encoding a "5'ALT-p16^{INK4A}" polypeptide or expression of a mutant "5'ALT-p16^{INK4A}" polypeptide, respectively, and that proliferation of the malignant cells is suppressed by "administering locally at a site of" the malignant cells "a polynucleotide encoding a 5'ALT-p16^{INK4A} polypeptide, said polynucleotide comprising SEQ ID NO:1 operatively linked to exons 2 and 3 of a p16 gene". The amendments are supported, for example, by previously pending claims 19 and 20 and claims 27 and 28, respectively, and at page 43, lines 8-12 (last sentence of first paragraph).

Claims 22 and 24, which depend from claim 18, and claims 30 and 32, which depend from claim 26, have been amended such that the language of the claims corresponds to that of the amended base claims. As such, the amendment to claim 13 merely addresses a formality.

New claims 34 to 36 have been added. New claim 34 is supported as discussed above with respect to the amendment to claim 1. New claim 35 is supported, for example, at page 72, last full paragraph. New claim 36 is supported, for example, at page 42, first full paragraph, and Table 1 (page 61).

B. Rejections under 35 U.S.C. § 112

The objection to the specification and corresponding rejection of claims 1, 7 to 9, and 12 to 23 under 35 U.S.C. § 112, first paragraph, as allegedly containing lacking enablement

It is stated in the Office Action that the claims read on any polypeptide containing the 5'ALT exon, but that there is no evidence provided that the 5'ALT exon by itself has activity, and that the specification only discloses two 5'ALT transcripts, including 5'ALT/p16^{INK4A}, which includes exons 2 and 3 of p16, and 5'ALT/p15^{INK4B}, which includes exon 2 of p15. It is further stated that there is no evidence in the specification that any protein is produced from the transcripts *in vivo*. Applicants point out that the claims have been amended to more specifically refer to polynucleotides comprising SEQ ID NO:1 (i.e., 5'ALT) operatively linked to exons 2 and 3 of p16; to polynucleotides comprising SEQ ID NO:1 (5'ALT) operatively linked to exon 2 of p15; and to polynucleotides encoding a 5'ALT/p16^{INK4A} polypeptide. As such, the claims no longer encompass any polynucleotide containing a 5'ALT sequence or any polypeptide containing a 5'ALT exon.

Applicants submit that there is no objective basis for the Examiner's questioning whether 5'ALT/p16^{INK4A} and/or 5'ALT/p15^{INK4B} polypeptides (hereinafter "5'ALT-polypeptides") are expressed in cells *in vivo*. Applicants point out that the specification discloses expression of transcripts comprising exons of the genes encoding the polypeptides, and further discloses that such transcripts are translated in an *in vitro* translation system. As such, it is submitted that the skilled artisan, viewing the specification, reasonably would have known that proteins encoded by the disclosed transcripts would be expressed *in vivo* in cells expressing the transcripts.

It is further stated in the Office Action that specification fails to provide a correlation between lack of expression of the 5'ALT-polypeptides and generation of a malignant hyperproliferative state, or that translation of a 5'ALT transcript shares any known activity of p16. Applicants point out, however, that the Liggett et al. reference, which was submitted with

application, a polynucleotide encoding a 5' ALT polypeptide can treat a malignant cell proliferative disorder. As discussed in the Preliminary Amendment, Liggett et al. demonstrate that introduction of a polynucleotide encoding p16β, which is the polypeptide referred to in the subject application as 5'ALT-p16, into cells of a head and neck squamous cell carcinoma (HNSCC) cell line or into HeLa cells resulted in growth inhibition of the tumor cells (see Liggett et al., Abstract). Significantly, the various HNSCC malignant cells are associated with expression of a mutant 5'ALT polypeptide (truncated) or with hypermethylation of the p16 promoter region (Liggett et al., Table 1, page 4120; see, similarly, Examples 6-10 of the specification, pages 59-67, disclosing methylation of p16 in HNSCC). Thus, the Liggett et al. reference demonstrates that introduction of a polynucleotide encoding a 5'ALT-p16 into HNSCC cells can inhibit the growth of the malignant cells, thus confirming that, as disclosed in the specification, a polynucleotide encoding a 5' ALT polypeptide can treat a malignant cell proliferative disorder.

It is also maintained in the Office Action that the claims are directed to *in vivo* gene therapy, the effect of which was unpredictable at the time the subject application was filed due, for example, to problems associated with poor efficiency of delivery and transient expression of the gene. Applicants point out that the claims have been amended to more clearly indicate that polynucleotide useful in a method of the invention is "administered locally at a site" of the cells to be treated. As such, there is no requirement, for example, of targeting a particular cell type, as the methods of the invention require delivery of the polynucleotide directly to the site of the cells to be treated. In this respect, Applicants submit that the results of Liggett et al. are particularly relevant because, while the experiments of Liggett et al. were performed *in vitro*, the experiments required directly contacting the cells with the polynucleotides, and, similarly, the claimed methods, while performed *in vivo*, require directly contacting the cells with the polynucleotides.

In summary, the claims have been amended to more clearly indicate that specific polynucleotides useful in practicing the methods, and to more clearly set forth administration of such polynucleotides locally to the site of cells to be treated. As such, it is submitted that one skilled in the art, viewing the specification, would have known that a method as claimed can treat a malignant cell disorder or suppress proliferation of malignant cells having the recited characteristics. It is further submitted that the Liggett et al. reference confirms that the specification was enabling for the claimed methods. Accordingly, it is respectfully requested that the objection to the specification be withdrawn and that the corresponding rejection of the claims under 35 U.S.C. § 112, first paragraph, be removed.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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Enclosure: Exhibit A

EXHIBIT A

MARKED UP COPY OF CLAIMS SHOWING THE AMENDMENTS

1. (Thrice amended) A method of treating a malignant cell proliferative disorder associated with decreased [expression] transcription of a 5'ALT polynucleotide comprising exon 2 of a p15 gene [or expression of a mutant 5' ALT polypeptide], the method comprising [contacting] administering locally at a site of cells having or suspected of having the disorder [with] a polynucleotide [encoding a 5'ALT polypeptide] comprising SEQ ID NO:1 operatively linked to a polynucleotide comprising exon 2 of the p15 gene, whereby expression of said polynucleotide restores transcription of the 5'ALT polynucleotide comprising exon 2 of the p15 gene [encoding a 5'ALT polypeptide suppresses proliferation of the cells], thereby treating the malignant cell proliferative disorder.

9. (Thrice amended) A method of treating a subject having a malignant cell proliferative disorder associated with [altered] decreased p16 expression due to methylation of a CpG island of a p16 gene in a cell, the method comprising administering [to] locally at a site of malignant cells exhibiting decreased p16 expression in a subject with the disorder, a therapeutically effective amount of a polynucleotide [encoding a 5'ALT polypeptide] comprising SEQ ID NO:1 operatively linked to exons 2 and 3 of the p16 gene, whereby expression of the polynucleotide in the malignant cells in the subject is restored [suppresses proliferation of the malignant cells], thereby treating the subject.

13. (Amended) The method of claim 1, wherein the polynucleotide [encoding a 5'ALT polypeptide] comprising SEQ ID NO:1 operatively linked to a polynucleotide comprising exon 2 of the p15 gene further comprises a colloidal dispersion system.

18. (Amended) A method of suppressing proliferation of malignant cells characterized by decreased expression of a polynucleotide encoding a [5'ALT] 5'ALT-p16^{INK4A} polypeptide, wherein said [5'ALT] 5'ALT-p16^{INK4A} polypeptide has tumor suppressor activity, the method comprising [contacting] administering locally at a site of the malignant cells [with] a polynucleotide encoding a [5'ALT] 5'ALT-p16^{INK4A} polypeptide, said polynucleotide comprising SEQ ID NO:1 operatively linked to exons 2 and 3 of a p16 gene, wherein expression of the 5'ALT-p16^{INK4A} polypeptide suppresses proliferation of the malignant cells.

22. (Amended) The method of claim 18, wherein the polynucleotide encoding [a 5'ALT] the 5'ALT-p16^{INK4A} polypeptide is contained in a vector.

24. (Amended) The method of claim 18, wherein the polynucleotide encoding [a 5'ALT] the 5'ALT-p16^{INK4A} polypeptide comprises a colloidal dispersion system.

26. (Amended) A method of suppressing proliferation of malignant cells characterized by expression of a mutant [5'ALT] 5'ALT-p16^{INK4A} polypeptide, wherein the mutant [5'ALT] 5'ALT-p16^{INK4A} polypeptide has decreased tumor suppressor activity, the method comprising [contacting] administering locally at a site of the malignant cells [with] a polynucleotide encoding a [5'ALT] 5'ALT-p16^{INK4A} polypeptide, said polynucleotide comprising SEQ ID NO:1 operatively linked to exons 2 and 3 of a p16 gene, wherein expression of the [5'ALT] 5'ALT-p16^{INK4A} polypeptide suppresses proliferation of the malignant cells.

30. (Amended) The method of claim 26, wherein the polynucleotide encoding [a 5'ALT] the 5'ALT-p16^{INK4A} polypeptide is contained in a vector.

32. (Amended) The method of claim 26, wherein the polynucleotide encoding [a 5'ALT] the 5'ALT-p16^{INK4A} polypeptide comprises a colloidal dispersion system.